Medical Science

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Prevalence and predictors of anemia among type 2 diabetic patients, single center study in Al-Madinah region, Saudi Arabia

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ABSTRACT

Background: Anemia is severe and common in diabetic patients compared to nondiabetic. Patients with type II Diabetes Mellitus (DM) are twice more likely to have anemia than nondiabetic patients and it is considered as a key prognostic factor. Studies indicate that anemia may increase the risk for progression of micro-and macro-vascular complications. The aim of this study was to determine the prevalence and predictors of anemia among patients with type II DM. *Methods*: This is a cross-sectional study conducted at diabetic center attached to king Fahad hospital included 6877 patients with a diagnosis of type II DM during the period 1st of March 2009 till 31st of July 2019. Patients were divided into two groups based on the presence or absence of anemia. *Results*: Out of 6877 patients included in the analysis, 4299 (62.5%) were males, 2332 (33.9%) were obese, 4386 (63.8%) had poor control of DM, 3795 (55.2%) had normal eGFR, 4904 (71.3%) were on metformin, 3745 (54.5%) were on insulin. The prevalence of anemia was 30%. About 24.1%of the patients had mild anemia, 4.1% had moderate anemia, 1.5% had severe anemia and 0.3% had life threating anemia. Multivariate analysis showed that female gender [OR, 2.7; 95% CI, 2.41-3.08; p<0.001], low eGFR [OR, 1.0; 95% CI, 0.97-0.97; p<0.001] were the predictors of anemia in type II DM patients. *Conclusion:* About 30% of patients had anemia. The predictors of anemia among type II DM patients were female gender and presence of advanced renal dysfunction. Early detection and treatment of anemia should be incorporated into the routine assessment of diabetic complications.

Keywords: Diabetes Mellitus, Anemia, metformin, insulin

1. INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder of great impact worldwide (Al-Nozha et al., 2004). The increasing prevalence of type II DM has become a

major public health concern (AlDallal & Jena., 2018). The worldwide prevalence of DM is 8.3%. In Saudi Arabia, the overall prevalence of DM was 23.7% during 2004 (Al-Nozha et al., 2004). However, by 2011 there had been a significant increase to 30%, with a rate of 34.1% in males and 27.6% in females (Alqurashi et al., 2011). Anemia is a common blood disorder. Patients with type II DM are twice more likely to have anemia than nondiabetic patients (AlDallal & Jena, 2018). Currently, the mechanisms proposed for the association between anemia and type II DM are complex and multifactorial, but there are many possible explanations. The presence of Renal Insufficiency (RI), the elevation of proinflammatory cytokines, nutritional deficiencies, concomitant autoimmune diseases, using drugs, and hormonal changes can contribute to cause anemia in diabetic patients (Al-Salman, 2014).

Previous studies have shown that the incidence of anemia in diabetic patients is mostly associated with the presence of RI. Hyperglycemia has increased the expression of proinflammatory cytokines such as IL-6, TNF- α, and NFκB which plays an essential role in insulin resistance. The IL-6 cytokine changes the sensitivity of the erythroid growth factor which is the progenitor to erythropoietin and promotes apoptosis of immature erythrocytes and consequently causing a reduction of circulating Hb (Barbieri et al., 2015).

Anemia was found to contribute to the development and progression of micro and macrovascular complications of DM, which has a negative impact on the quality of life (Al-Salman, 2014). Therefore, it is important to diagnose and correct anemia early to optimize the outcomes in diabetic patients. Thus, the aim of this study is to determine the prevalence and predictors of anemia among patients with type II DM in Al Madinah, Saudi Arabia.

2. MATERIAL AND METHODS

Study Design, Study Setting and Study Period

This is a cross-sectional study of Saudi diabetic patients, who had been following the diabetic center at King Fahad Hospital (KFH), Al-Madinah. The patients registered in the Health Management Information Systems (HMIS) database during the period from 1st of March 2009 till 31st of July 2019.

Study Population

We reviewed the electronic medical records from the HMIS. A total of 11742 patients were identified as having a documented clinical diagnosis of type II DM. Patients were considered to have type II DM based on serum Hemoglobin A1c (HbA1c) ≥ 6.5% or have at least one for the diagnostic criteria for type II DM as the following: two readings of fasting plasma glucose ≥ 7 mmol/l [126 mg/dl], 2-hours oral glucose tolerance test or random blood glucose ≥ 11.1 mmol/l [200 mg/dl] along with diabetic symptoms (Care, and Suppl, 2018). According to glycemic status, the patients were divided into controlled group with HbA1c level less than or equal to 7.5% and poorly controlled group with HbA1c level more than or equal to 7.5% (Al Dallal and Jena, 2018).
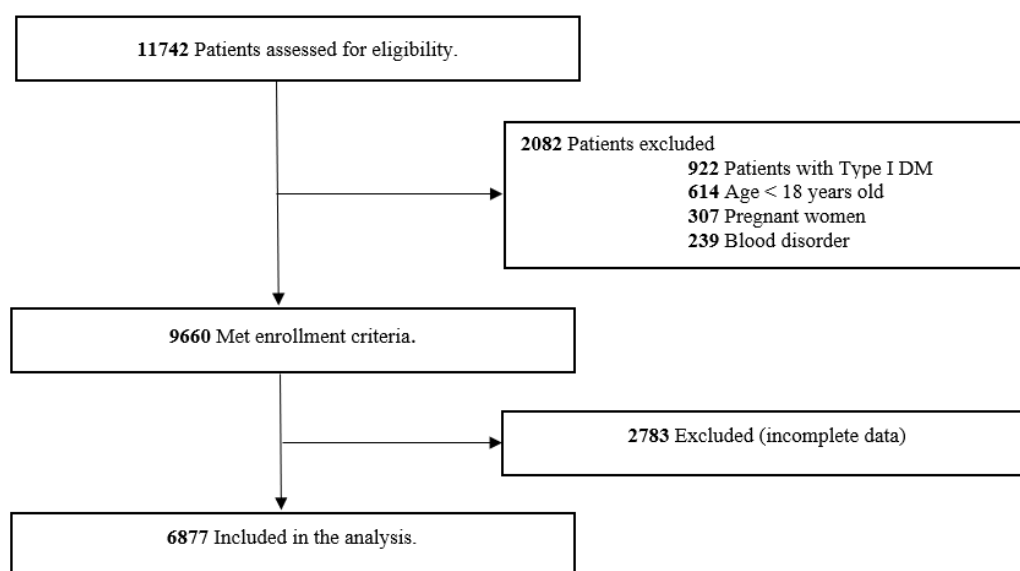

Figure 1 Flow chart of the study population

Patients with type II DM or gestational DM were excluded. Age less than 18 years old, pregnant females, patients with malignancy, patients with hereditary blood disorders, patients with blood loss or donated blood recently were set as an exclusion criterion as well. Of the remaining 9660 patients, we excluded 2783 patients with incomplete data, yielding 6877 patients for analysis (Figure 1).

Measurements

Anemia was defined as Hb level <13 g/dl and <12 g/dl in males and females respectively, according to the world health organization's criteria for anemia. Anemia was classified according to severity into mild anemia when Hb level is 9.5 -12.9 g/dL in males, and 9.5 - 11.9 g/dL in females, moderate anemia when Hb is 8.0 - 10.9 g/dL, severe anemia when Hb is 7.9 - 6.5 g/dL, and life-threatening anemia when Hb is ≤ 6.5. In the morphologic classification, anemia was subdivided into normocytic normochromic when Mean Corpuscular Volume (MCV) 80–95 fL and Mean Corpuscular Hemoglobin (MCH) ≥27p, microcytic hypochromic when MCV <80fL and MCH <27pg, and macrocytic when MCV >95fL (Idris et al., 2018).

Glomerular Filtration Rate (GFR) was estimated depending on the equation made by the chronic kidney disease epidemiology collaboration as the following: eGFR = 141 × min (Scr / κ, 1)α × max (Scr / κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] where: Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males (Stevens et al., 2011). All patients were divided according to the current national kidney foundation kidney disease outcomes quality initiative recommendations into five renal function categories with eGFR (mL/min/ 1.73 m2): Stage I (eGFR ≥90, normal function), Stage II (eGFR 60–89, mild dysfunction), Stage III (eGFR 30–59, moderate dysfunction), Stage IV (eGFR 15–29, severe dysfunction) and Stage V (eGFR <15, end stage renal disease) (Idris et al., 2018).

Ethical Approval

The research ethics committee of Taibah university and the ethical committee board of KFH approved this study protocol (approval number: IRB00010413). All study parts were conforming to the declaration of Helsinki Ethical Principles for medical research involving human subjects as revised in 1975.

Statistical Analysis

All the data were manually checked for its clarity and completeness, then coded in an excel file, entered, and transported to Statistical Package for Social Science (SPSS) software version 23 for analysis. Continuous data were presented as mean ± Standard Deviation (SD) as they were normally distributed when tested by the Shapiro-Wilk test, while the categorical data were presented as frequencies and percentages. Baseline demographic and clinical variables were compared between two groups by using the Pearson chi-squared test for categorical variables. To assess whether the continuous variables differed among the study two groups, we used the independent sample t-test. The predictors of type II DM were determined by using binary logistic regression. P-value was considered significant if it is ≤ 0.05.

3. RESULT

Out of 6877 patients included in the analysis, 4299 (62.5%) were males, 2332 (33.9%) were obese, 4386 (63.8%) had poor controlled DM, 3795 (55.2%) had normal eGFR, 4904 (71.3%) were on metformin, 3745 (54.5%) were on insulin, and 4714 (68.5%) were on statin. Up to 2059 (30.0%) of diabetic patients had anemia. About 1656 (24.1%) of the patients had mild anemia, 283 (4.1%) had moderate anemia, 102 (1.5%) had severe anemia and 18 (0.3%) had life threating anemia. Among the anemic patients, 5175 (75.3%) had normocytic normochromic anemia, 1585 (23.0%) had Microcytic hypochromic anemia, while 117(1.7%) had Macrocytic anemia (Table 1).

Table 1 Sociodemographic and Clinical Characteristics of the Study Population

Variables	Number (n=6877)	(%)
Gender		
Male	4299	(62.5)
Female	2578	(37.5)
Body mass index (kg/m²)		
Underweight (<18.5)	30	(0.4)
Normal (18.5-24.9)	2204	(32)

Overweight (≥25-29.9)	2311	(33.6)
Obese (≥30)	2332	(33.9)
Glycemic status		
Well control (=<7.5)	4386	(63.8)
Poor control (>7.5)	2491	(36.2)
Severity of anemia		
Mild anemia ((Hb 9.5–10.9 g/dl)	1656	(24.1)
Moderate anemia (Hb 8–9.4 g/dl)	283	(4.1)
Severe anemia (Hb 6.5–7.9 g/dl)	102	(1.5)
Life Threatening anemia	18	(0.3)
Classification of anemia based on morphology		
Normocytic normochromic	5175	(75.3)
Microcytic hypochromic	1585	(23.0)
Macrocytic	117	(1.7)
CKD stages		
Normal GFR (eGFR > 90 mL/min)	3795	(55.2)
Mild CKD (eGFR = 60-89 mL/min)	1573	(22.9)
Moderate CKD (eGFR = 30-59 mL/min)	887	(12.9)
Severe CKD (eGFR = 15-29 mL/min)	302	(4.4)
End Stage CKD (eGFR <15 mL/min)	320	(4.7)
Medications		
Insulin	3745	(54.5)
Metformin	4904	(71.3)
Gliclazide	3195	(46.5)
Aspirin	4087	(59.4)
Statin	4714	(68.5)
eGFR; estimated Glomerular Filtration Rate. CKD; chronic kidney disease		

Anemic patients were significantly older. Mean ± SD of age was 63±13 years in anemic patients compared to 58±12 years in patients without anemia (p<0.001). Anemic patients were significantly females (p<0.001), had BMI ≥ 30 (p<0.001), poorly controlled type II DM (p<0.001), had advanced CKD stage (p<0.001). Medical therapy has differed between anemic and non-anemic patients. Using insulin, metformin, gliclazide, aspirin, and statin were lower in anemic patients (p<0.001). The prevalence of anemia was increased as stages of CKD increased, particularly those with stage IV and V CKD (Table 2). (Figure 2) showed that the prevalence of anemia was 17.7%, 28.5%, 49.8%, 78.5%, 80.9% in patients with Stage I CKD to V, respectively.

Table 2 Baseline clinical characteristics of Study Population (n=6877), Stratified by anemi

Variables	With anemia (n=2059) (29.9%)		Without anemia (n=4818) (70.1%)		OR (95% CI)		P value
	Number (%) / Mean± SD						
Age	63 ±13		58±12				<0.001
Gender							
Female	978	(37.9)	1600	(62.1)	1.82	(1.638-2.022)	<0.001
Male	1081	(25.1)	3218				
Body mass index (kg/m²)							
Underweight (<18.5)	8	(26.7)	22	(73.3)			<0.001
Normal (18.5-24.9)	806	(36.6)	1398	(63.4)			
Overweight (≥25-29.9)	646	(28.0)	1665	(72.0)			
Obese (≥30)	599	(25.7)	1733	(74.3)			
Glycemic status							

|							
Well control (=<7.5)	1270	(29.0)	3116	(71.0)	1.13	(1.022-1.265)	<0.001
Poor control (>7.5)	789	(31.7)	1702	(68.3)			
CKD stages							
Stage 1 (eGFR > 90 mL/min)	673	(17.7)	3122	(82.3)			
Stage 2 (eGFR 60-89 mL/min)	448	(28.5)	1125	(71.5)			
Stage 3 (eGFR 30-59 mL/min)	442	(49.8)	445	(50.2)			<0.001
Stage 4 (eGFR 15-29 mL/min)	237	(78.5)	65	(21.5)			
ESRD (eGFR < 15 mL/min)	259	(80.9)	61	(19.1)			
Medications							
Insulin	1346	(35.9)	2399	(64.1)	1.90	(1.711-2.118)	<0.001
Metformin	1180	(24.1)	3724	(75.9)	0.39	(0.353-0.440)	<0.001
Gliclazide	819	(25.6)	2376	(74.4)	0.679	(0.611-0.754)	<0.001
Aspirin	1401	(34.3)	2686	(65.7)	1.69	(1.516-1.884)	<0.001
Statin	1516	(32.2)	3198	(67.8)	1.41	(1.261-1.586)	<0.001
CKD; chronic kidney disease, eGFR; estimated Glomerular Filtration Rate.							
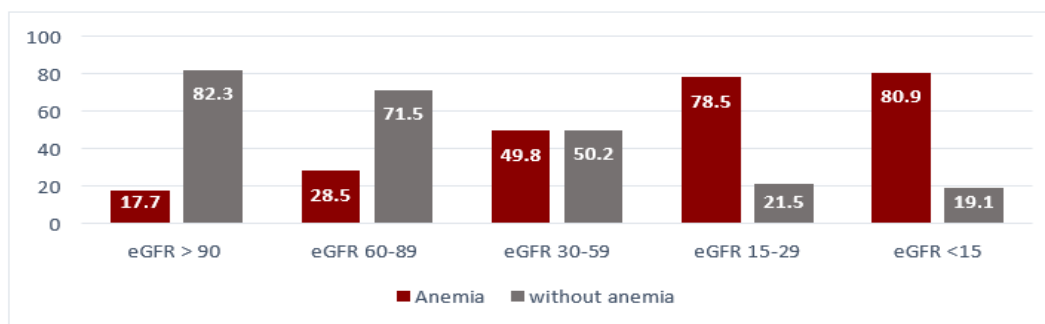
Figure 2 Prevalence of anemia among type II DM regarding toCKDs stages.

Regarding laboratory data, the mean Hb level was 10.73 ± 1.56g/dl in anemic patients compared to 14.37 ± 1.46 g/dl in non-anemic patients (p <0.001). Mean HbA1C was about 8.1 in both groups (p <0.84). Anemic patients exhibited significantly worsening kidney function tests. Mean eGFR was 65.67 ± 42.45mL/min in anemic patients compared to 98.79 ± 34.10 mL/min in non-anemic patients (p <0.001). Higher levels of serum creatinine and blood urea nitrogen were also observed in anemic patients. Detailed laboratory data are shown in (Table 3).

Table 3 Continuous characteristics of the study population stratified by presence or absences of anemia

Variable	With anemia (n=2059) (29.9%)	Without anemia (n=4818) (70.1%)	P value
	Mean ± SD		
CBC			
Haemoglobin (g/dl)	10.73 ± 1.56	14.37 ± 1.46	<0.001
HCT%	33.20 ± 4.77	43.05 ± 4.17	<0.001
RBC ×10^{12}/μL	4.29 ± 6.91	5.20 ± 4.74	<0.001
MCV fL	82.45 ± 8.36	84.54 ± 5.49	<0.001
MCH	28.28 ± 2.34	26.68 ± 68	<0.001
MCHC	32.34 ± 2.83	33.46 ± 1.83	<0.001
RDW	15.3 ± 3.41	13.46 ± 2.32	<0.001
WBC ×10^3/μL	8.69 ± 4.35	7.94 ± 2.67	<0.001
Platelet Count ×10^3/μL	285.40 ± 116.45	267.47 ± 75.04	<0.001
HbA1c (%)	8.19 ± 1.85	8.13 ± 1.58	0.840
Random glucose (mmol/L)	9.97 ± 5.05	10.13 ± 4.80	0.051

Kidney Function Test			
eGFR	65.67 ± 42.45	98.79 ± 34.10	<0.001
Creatinine (µmol/L)	190 ± 203.60	92.27 ± 75.46	<0.001
BUN (mmol/L)	11.14 ± 8.14	6.08 ± 3.57	<0.001
Uric Acid (µmol/L)	350.60 ± 123.48	314.27 ± 88.32	<0.001
Liver function test			
AST (U/L)	23.08 ± 7.69	24.61 ± 7.99	0.888
ALT (U/L)	25.18 ± 12.61	27.19 ± 25.08	0.704
Total bilirubin (µmol/L)	10.31 ± 6.67	10.65 ± 7.62	0.190
Albumin (g/L)	36.72 ± 5.03	36.71 ± 5.15	0.994
Lipid profile			
Cholesterol(mmol/L)	3.90 ± 1.37	4.38 ± 1.21	<0.001
Triglycerides(mmol/L)	1.61 ± 1.09	1.80 ± 1.19	<0.001
Electrolytes			
Sodium (mmol/L)	136.88 ± 5.77	137.76 ± 3.80	<0.001
Potassium7(mmol/L)	4.34 ± 0.74	4.13 ± 0.52	<0.001
Chloride (mmol/L)	102.51 ± 6	101.75 ± 3.92	<0.001
Calcium (mmol/L)	2.01 ± 0.15	2.02 ± 0.15	0.231
CBC; Complete blood count, HCT%; Hematocrit, RBC; Red Blood Cells, MCV; Mean Corpuscular Volume, WBC; White Blood Cells, BUN; Blood Urea Nitrogen, eGFR; estimated Glomerular Filtration Rate			

Multivariate analysis showed that female gender [OR, 2.7; 95% CI, 2.4-3.08; p<0.001], low eGFR [OR, 1.0; 95% CI, 0.97-0.97; p<0.001], and using insulin [OR, 1.4; 95% CI, 1.21-1.54; p<0.001], were the risk factors of anemia (Table 4).

Table 4 Predictors of Anemia among DM patients (n=6877)

Variables	Sig	Exp(B)	95%C.I.for EXP(B)	
			Lower	Upper
Female	<0.001	2.72	2.41	3.08
eGFR	<0.001	0.97	0.97	0.97
Aspirin	0.287	1.07	0.94	1.21
Statin	0.171	0.89	0.77	1.04

4. DISCUSSION

Anemia in patients with Type II diabetes is an increasingly recognized entity and potentially contributing to increase risk of developing diabetes complications (Sharif et al., 2014). It is also reported that patients who have anemia along with diabetes have relatively less life span than diabetic patients without anemia by increasing the risk of hospitalization and premature death (Panda & Ambade, 2014; AlDallal & Jena, 2018). Despite these facts, anemia is unrecognized in 25% of the diabetic patients (Abate et al., 2013). In the current study, we found that about 30% of diabetic patients were anemic. In accordance with the results of the current study, a retrospective study carried out in Kuwait enrolled 19059 diabetic patients, which revealed that 29% of diabetic patients had anemia (AlDallal & Jena, 2018). Also, a study involved 722 diabetic patients showed that about 23% of patients had anemia (Thomas et al., 2005). Bonakdaran et al., (2011) reported that 19% of diabetic patients had anemia. Adejumo et al., (2012) showed that 15% of diabetic patients had anemia. However, cross-sectional studies done by Panda & Ambade, (2014) showed a higher prevalence of anemia among diabetic patients. They showed that about 63% of diabetic patients had anemia.

The current study showed that most of the patients had mild anemia and about 75% of anemic patients had normocytic normochromic anemia which may be due to the chronicity of the DM. Similarly, a cross-sectional study conducted in Malaysia showed that 61% of the anemic patients had mild anemia and 58% had a morphological classification of normocytic normochromic anemia (Idris et al., 2018). DM can cause anemia through different pathophysiological mechanisms. Symptomatic autonomic neuropathy is a complication of poor glycemic control and can lead to denervation of the efferent sympathetic pathways of the patient's kidneys which resulting in the loss of required erythropoietin production. Using metformin for a long time can lead to vitamin B12 deficiency anemia (Panda & Ambade, 2014). In poorly controlled diabetic patients, the erythrocyte precursors prone to

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prolonged direct glucose toxicity. Also, the mature erythrocytes can be affected by oxidative stress leading to disturbances in the erythrocyte function (AlDallal & Jena, 2018). Other factors which have been reported to increase the risk of anemia include systemic inflammation damage to renal architecture produced by chronic hyperglycemia and consequent formation of advanced glycation end products. It is speculated that these conditions may be aggravated in poorly controlled diabetes than in controlled diabetes (Adejumo et al., 2018).

The current study found that the independent predictors of anemia in diabetic patients were female gender and higher stage of CKD. This finding is consistent with previous studies. Alsayegh et al., (2017) found that the higher prevalence of anemia was in diabetic female patients. It was 35% and 21% in females and males, respectively. Similarly, Sharif et al., (2014) showed that the prevalence of anemia was 36% in females compared to 27% in males. This may explain by the fact that females lose some blood during mensuration cycles, so they are more prone to have anemia. However, some studies revealed that males were more vulnerable than females (Panda & Ambade, 2018; Griac et al., 2015).

Anemia is an important marker of CKD which occurs earlier in the progression of diabetic kidney disease and perhaps more severe than formerly realized. In patients with diabetes, anemia may be the result of decreased erythropoietin production by the failing kidney (Panda & Ambade, 2014). Idris et al., (2018) found that anemia was higher among patients with stage III CKD and above and they also recommended that patients with CKD stage III should be screened for anemia yearly and more often for those with CKD stage IV and V. The current study found that 45% of patients with GFR<60 mL/min/ 1.73m² had anemia. Al-Salman, (2014) reported that the prevalence of anemia in diabetic patients was correlated with renal impairment. Amongst patients with impaired renal function, 64.7% had anemia while 35.3% had no anemia. Also, he found that the percentage of anemic patients with GFR<60 mL/min/ 1.73m² was 46%, which was like the current study findings.

5. CONCLUSION

About 30% of the patients had anemia. Female gender and advanced CKD stage were independent predictors of anemia in type II DM. Anemia have a great significant adverse effect on the quality of life of diabetic patients. It is associated with increasing the risk of diabetic complications. Early detection and treatment are important to improve prognosis in diabetic patients.

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